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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,954	06/25/2001	Hubert Jan Jozef Loozen	O/98414-US	9900

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AKZO NOBEL INC.
INTELLECTUAL PROPERTY DEPARTMENT
120 WHITE PLAINS ROAD 3RD FLOOR
TARRTOWN, NY 10591

EXAMINER	
COTTON, ABIGAIL MANDA	
ART UNIT	**PAPER NUMBER**
1617	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/831,954	LOOZEN ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,8 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7-8 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment and remarks submitted on February 20, 2007. Claims 1, 7-8 and 13 are pending in the application and are being examined on the merits herein.

The objection to claims 2 and 14 is being withdrawn in view of the cancellation of these claims. The rejection of claims 1-2, 4, 7, 13-14 and 16 under 35 U.S.C. 112, second paragraph, is also being withdrawn, in view of Applicants' amendment to recite the specific R11 groups as in claims 1, 8 and 13, and cancellation of claims 2 and 14.

Applicants' arguments regarding the rejections of the claims over the prior art have been fully considered, but have not been found persuasive. The following rejections have been required by Applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 7-8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article entitled "Steroidal Affinity labels of the Estrogen Receptor. 3. Estradiol 11ß-n-Alkyl Derivatives Bearing a Terminal Electrophilic Group: Antiestrogenic and Cytotoxic Properties" by Lobaccaro et al, 1997 (of record)

Lobaccaro et al. teaches the development of a new series of steroidal affinity labels of the estrogen receptor, including 11Beta-ethyl (C_2), 11Beta-butyl (C_4) and 11Beta-decyl (C_{10}) derivatives of estradiol (see abstract, in particular.) Lobaccaro et al. teaches the synthesis of compounds having the formula I wherein R11 is butene or ethene (see compounds 5a-5B, Scheme 1 on page 2218, in particular) and teaches testing of the binding of the butene derivative of estradiol 5b and its binding to the estrogen receptor, as well as its activity as an estrogen agonist (see Tables 1 and 2, in particular.) Lobaccaro et al. also refers to the compound 5b as being "estrogenic," i.e., and estrogen agonist (see paragraph bridging pages 2221-2222, in particular.) Lobaccaro et al. also generally concludes that for estradiol 11Beta-substituted derivatives, the size of the 11beta alkyl side chain is what affects the estrogenic vs. antiestrogenic activity, rather than the size of the whole substituent or the type of electrophillic group substituted on the side chain (see page 2223, first full paragraph, in particular.) Lobaccaro et al. teaches that the compounds having affinity for the estrogen receptor may have use in the treatment of estrogen receptor-containing mammary tumors (see paragraph bridging left and right hand columns, page 2223, in particular),

and thus teaches the use of compounds that bind the estrogen receptor in a pharmaceutical composition or for pharmaceutical treatment.

Lobaccaro et al. does not specifically teach the estrogenic compound having the group R_{11} that is one of the particular chains that is a pentene, pentane, pentyl group or butene group substituted with a cyclopropyl group, as recited in claims 1, 8, and 13.

However, as the compound 5b of Lobaccaro et al. differs from the instantly recited compounds by only a methylene or ethylene group, that is, Lobaccaro teaches a C4 chain whereas the instant compounds include C5 chains, it is considered that the instantly claimed compounds are homologous to the compound of Lobaccaro et al, and thus are expected to have similar properties to the compound as taught by Lobaccaro et al, such as estrogenic activity. Thus it is considered that one of ordinary skill in the art would have found it obvious to provide the C5 homologs of the Lobaccaro et al. C4 compound, with the expectation of providing a compound with similar properties. See *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977.)

Furthermore, as Lobaccaro et al. teaches that the length of the 11beta alkyl side chain can effect the estrogenic/antiestrogenic activity, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of length of the 11beta alkyl side chain of the compound, according to the guidance provided by Lobaccaro et al, to provide a

composition having desired properties. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, the pharmaceutical composition of claim 1, and the steroid compound of claim 13 are considered to be obvious over the teachings of Lobaccaro et al. Regarding the recitation the compound has "ERalpha agonist activity and ERbeta antagonist activity," as recited in claims 1 and 13, it is respectfully pointed out that the recitations have not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *in re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152 88 USPQ 478, 481 (CCPA 1951.)

Regarding the methods of claims 7 and 8, Lobaccaro et al. teaches that the estrogen compounds can be used to treat estrogen-receptor containing mammary tumors, as discussed above, and renders obvious providing the compounds as recited in the claims, and thus teaches a method of treating estrogen deficiency disorders (i.e. tumors that can be treated by providing an estrogen, and thus are "estrogen deficient")

by providing a therapeutic amount of the compound and inducing either ERalpha agonist or ERbeta antagonist activity, as recited in the claims. It is furthermore noted that that the agonist and/or antagonist activity of a compound is a property thereof, and a product and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Accordingly, the composition and method rendered obvious by the references would, absent evidence to the contrary, meet the limitations pertaining to the ERalpha and ERbeta agonist or antagonist activity used therein.

It is furthermore noted that, as Lobaccaro et al. teaches that the compounds having affinity for the estrogen receptor, it would have been obvious to one of ordinary skill in the art to provide such compounds for the treatment of disorders resulting from the deficiency of such estrogenic compounds, as recited in claims 7 and 8, with the expectation that providing the estrogenic compound would reduce the estrogen deficiency.

Claims 1, 7-8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article entitled "11ß-Substituted Estradiol Derivatives. 2. Potential Carbon-11-Iodine-Labeled Probes for the Estrogen Receptor" by Napolitano et al, 1995 (of record.)

Napolitano et al. teaches 11ß-substituted derivatives of estradiol including ethynyl and propynyl derivatives (see abstract, in particular.) Napolitano teaches that the compounds have high affinity for the estrogen receptor, and provides the affinities

for compounds 2a (entry 3) having a propynyl group and entry 11 having an ethene group (see Table 1, in particular.) Napolitano et al. teaches that the length of the chain of the 1-alkynyl group at the 11beta position affects the binding affinity of the compounds, with the shorter chain having a great affinity (see page 2776, first full paragraph of conclusion section, in particular.) Napolitano et al. teaches that the compounds can be used as tumor-imaging radiopharmaceuticals (see first full paragraph of Introduction section, in particular), and thus teaches providing a pharmaceutical composition having the compounds, as recited in claim 1.

Napolitano et al. does not specifically teach the estrogenic compound having the group R_{11} that selected from one of the particular chains that is a pentene, pentane, pentyl group or butene group substituted with a cyclopropyl group, as recited in claims 1, 8, and 13.

However, as the compounds 2a and entry 11 of Napolitano et al. differs from the instantly recited compounds by only an ethylene group (-CH2-CH2-), that is, Napolitano et al. teaches a C2 or C3 chain whereas the instant compounds include C5 chains, it is considered that the instantly claimed compounds are homologous to the compounds of Napolitano et al, and thus are expected to have similar properties to the compounds as taught by Napolitano et al, such as estrogen receptor binding activity. Thus it is considered that one of ordinary skill in the art would have found it obvious to provide the C5 homologs of the Napolitano et al. C2 or C3 compound, with the expectation of

providing a compound with similar properties. See *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977.)

Furthermore, as Napolitano et al. teaches that the length of the 11beta alkynyl side chain can effect the estrogen receptor binding affinity, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of length of the 11beta alkynyl side chain of the compound, according to the guidance provided by Napolitano et al, to provide a composition having desired properties, such as desired estrogen receptor binding affinities. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, the pharmaceutical composition of claim 1, and the steroid compound of claim 13 are considered to be obvious over the teachings of Napolitano et al. Regarding the recitation the compound has "ERalpha agonist activity and ERbeta antagonist activity," as recited in claims 1 and 13, it is respectfully pointed out that the recitations have not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *in re Hirao*, 535 F.2d

67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152 88 USPQ 478, 481 (CCPA 1951.)

Regarding the methods of claims 7 and 8, Napolitano et al. teaches that the estrogen compounds can be used as radiopharmaceuticals to image tumors, as discussed above, and renders obvious providing the compounds as recited in the claims. It is furthermore noted that Napolitano et al. teaches that the compounds have affinity for the estrogen receptor, and thus have estrogenic activity. Accordingly, it is considered that one of ordinary skill in the art would have been motivated to provide such compounds for the treatment of disorders resulting from the deficiency of such estrogenic compounds, as recited in claims 7 and 8, with the expectation that providing the estrogenic compound would reduce the estrogen deficiency. It is furthermore noted that that the agonist and/or antagonist activity of a compound is a property thereof, and a product and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Accordingly, the composition and method rendered obvious by the references would, absent evidence to the contrary, meet the limitations pertaining to the ERalpha and ERbeta agonist or antagonist activity used therein.

Response to Arguments

Applicants' arguments filed February 20, 2007 have been fully considered but they are not persuasive.

Applicants' argue that the compound 5b taught by Lobaccaro et al. "was just used as a reference compound," and not as a steroidal affinity label, and thus was not the primary focus of Lobaccaro et al's work (see page 8 of Remarks submitted February 20, 2007.) The Examiner agrees that the primary focus of Lobaccaro et al's work is the development of 11Beta-alkyl derivatives of estradiol wherein the alkyl group is further substituted by an electrophilic group for affinity labeling purposes. However, the Examiner notes that Lobaccaro et al. nonetheless teaches that the compound 5b, which is alkyl substituted (butene group) without an electrophilic group, is "estrogenic," i.e an estrogen agonist, and teaches binding affinities for the estrogen receptor (see pages 2221-2222 and Tables 1 and 2, in particular.) Accordingly, it is considered that one of ordinary skill in the art would have found it obvious to provide a C5 homolog in the place of the C4 compound taught by Lobaccaro et al, with the expectation of achieving a compound having some estrogenic activity.

Applicants further argue that the claimed compounds are not obvious over the teaching of Lobaccaro et al, because the claimed compounds "do not posses similar properties to the compound taught by Lobaccaro et al" (see page 8 of Remarks submitted February 20, 2007. In particular, Applicants point to Table B of their specification which they assert shows ERα agonist/ERβ agonist activity for compound 2, which they assert is compound 5b of Lobaccaro et al, and which is in contrast to compound 3, (included in the compounds recited in claim 1), having ERα agonist/ERβ antagonist activity. The Examiner notes that the motivation for providing the C5

homolog in place of the 5b compound of Lobacarro et al. rests on an expectation of similar biological activity due to the close chemical structure of the two compounds, and in particular on similar ER agonist activity (Lobaccaro et al. does not specify whether the estrogen receptor is ERα or ERβ.) The results shown by Applicants in Table B of their specification actually confirm this assumption, as both the compound 5b and the C5 homolog exhibit ERα agonist activity. Accordingly, it is considered that one of ordinary skill in the art at the time of the invention would have found it obvious to provide the homolog with the expectation of achieving an "estrogenic" compound.

Furthermore, it is noted that Applicants determine the compounds tested in Table B to be ERα or Erβ agonist or antagonists by assigning them a rating of "(-) which means that it does not satisfy the ER affinity profile of the present invention, while (+) means a compound according to the invention, i.e. an agonist ERα and an antagonist for Erβ" (see page 13 of specification.) Applicants do not teach how they arrived at the determination of agonist or antagonist activity, such as what magnitude of the activity was deemed sufficient to warrant the label of "agonist" or "antagonist", and thus it cannot be reasonably determined whether the difference in the magnitude of the asserted "agonism" and "antagonism" is of sufficient degree to show unexpected results between the compounds. It is noted that a showing of unexpected results must be based on evidence, not argument or speculation. In re Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997).

Regarding Applicants' assertion that the claimed compounds are not obvious over the teachings of Lobaccaro et al. because Lobaccaro et al. is not directed to compounds having ERα agonist and Erβ antagonist activity, it is noted that, as stated by Applicants, Lobaccaro et al. does not distinguish between ERα and Erβ receptors, and instead merely teaches binding affinity for a "cytosolic estrogen receptor," and thus the activity of the compounds of Lobaccaro et al. with regards to the individual alpha and beta receptors cannot be determined from the disclosure of Lobaccaro et al, all that is known is that the compound 5b of Lobaccaro et al. is "estrogenic," and thus is an agonist for at least one of the types of estrogen receptors. It is furthermore noted that as the teachings of Lobaccaro et al. render the claimed C5 homolog obvious, the property of such a claimed compound will also be rendered obvious by the prior art teachings, since the properties, namely the receptor binding agonism/antagonism, are inseparable from its composition. Therefore, if the prior art teaches the compound or renders the compound obvious, then the properties are also taught or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

Regarding Napolitano et al, Applicants argue that Napolitano et al. is "merely concerned with designing high-affinity probes for estrogen receptor imaging," (see page 10 of Remarks submitted February 20, 2007), and is not concerned with pharmaceutical

compositions for treating estrogen deficiency disorders. The Examiner respectfully disagrees. The Examiner notes that Napolitano et al. teaches that the compounds are suitable as radio-pharmaceuticals, as discussed above, and thus teaches providing the compounds as pharmaceutical products. Furthermore, for the compounds and compositions containing the 11 beta substituted estradiol, as recited in claims 1 and 13, the intended use of the compounds as recited in the preamble is not given patentable weight, as is also discussed above. Also, as Napolitano et al. teaches that the compounds have affinity for the estrogen receptor, and thus have estrogenic activity, it is considered that one of ordinary skill in the art would have found it obvious to provide the compounds for the treatment of disorders resulting from the deficiency of estrogenic compounds, as recited in claims 7 and 8, with the expectation of reducing the estrogen deficiency, as discussed above.

Applicants' further pointed out typographical errors in the Examiners rejection, namely that the Examiner had referred to compound 3a in Table 1 as having a propynyl group, when in fact compound 2a is the correct entry having the propynyl group, and compound 11 as having an ethynyl group, when in fact the entry contains an ethenyl group. The Examiner has corrected the typographical errors in the rejection above, and appreciates Applicants' assistance in pointing out the correct compound identifications.

Applicants' further argue that Napolitano et al. teaches against lengthening the 11beta alkyl chain, because Napolitano et al. teach that the compound having the

ethynyl group has a greater affinity than the compound having the propynyl group. The Examiner notes that Napolitano et al. teaches that the compound having the propynyl group does indeed have estrogen binding affinity, even though this affinity is reduced. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of the length of the alkynyl side-chain provided in the composition, according to the guidance provided by Napolitano, to provide a compound having a desired binding affinity. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.) The mere fact that an 11Beta-estradiol derivative having a longer chain may not bind with as high an affinity as derivatives having an ethynyl or propynyl group is not considered to be a sufficient teach against providing the longer chain derivatives, as the longer chain derivates would still be expected to have some, if not the highest, binding affinity.

Applicant furthermore argue that Napolitano et al. does not specifically teach that the compounds are Erα agonists/Erβ antagonists, as recited in the claims. However, it is noted that as the teachings of Napolitano et al. render the claimed C5 homolog obvious, the property of such a claimed compound will also be rendered obvious by the prior art teachings, since the properties, namely the receptor binding agonism/antagonism, are inseparable from its composition. Therefore, if the prior art teaches the compound or renders the compound obvious, then the properties are also

taught or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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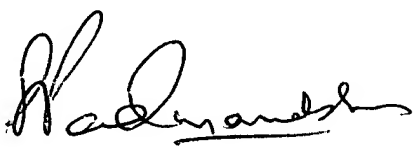

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER